

# Literature Report IX

## Palladium-Catalyzed Divergent Enantioselective Functionalization of Cyclobutenes

Reporter: Tong Niu

Checker: Bao-Qian Zhao

Wang, Z.; Zhu, J.; Wang, M.; Lu, P., *J. Am. Chem. Soc.* 2024, 146, 12691

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● 2024.06.11 ●

# CV of Prof. Ping Lu (陆平)

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## Education & Professional Experience:

- ❑ **1999-2004** B.S., USTC
- ❑ **2004-2009** Ph.D., SIOC (Prof. Shengming Ma)
- ❑ **2010-2012** Postdoc., TUM (Prof. Thorsten Bach)
- ❑ **2012-2016** Postdoc., UCSB (Prof. Armen Zakarian)
- ❑ **2016-2022** Associate Professor, Tenure-Track, FDU
- ❑ **2022-Present** Professor, FDU

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## Research

- ❑ Synthesis of Bioactive Compounds and Natural Products
- ❑ Synthesis of Strained Molecules and Applications: cycloaddition, functionalization and applications of strain releasing of small-ring intermediates

# Contents

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## 1 Introduction

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## 2 Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

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## 3 Summary

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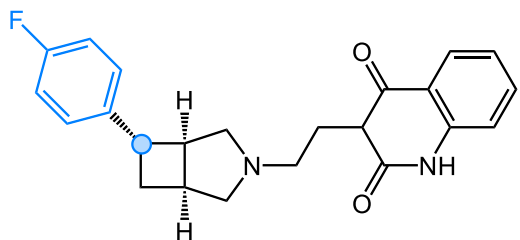
# Introduction

“Escape from Flatland”

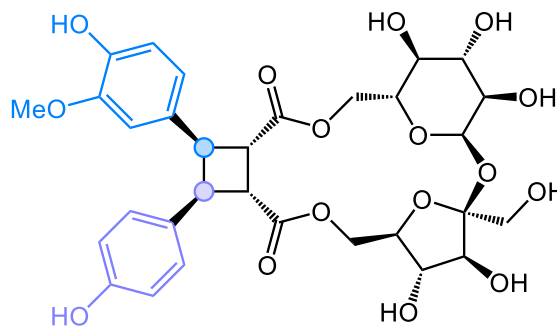


Aliphatic Small Rings—Increasingly Investigated

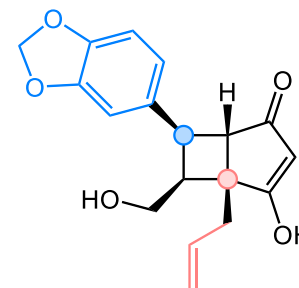
## Representative Bioactive Cyclobutanes



belaperidone

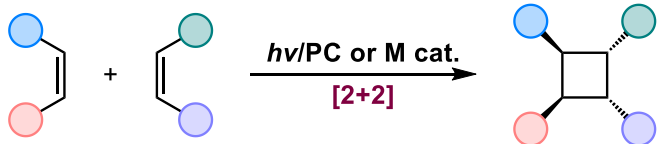


trigohonbanoside D

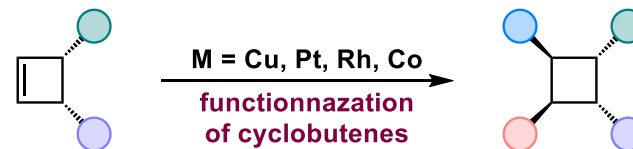


madangone B

## Construction of Enantiomerically Enriched Cyclobutanes

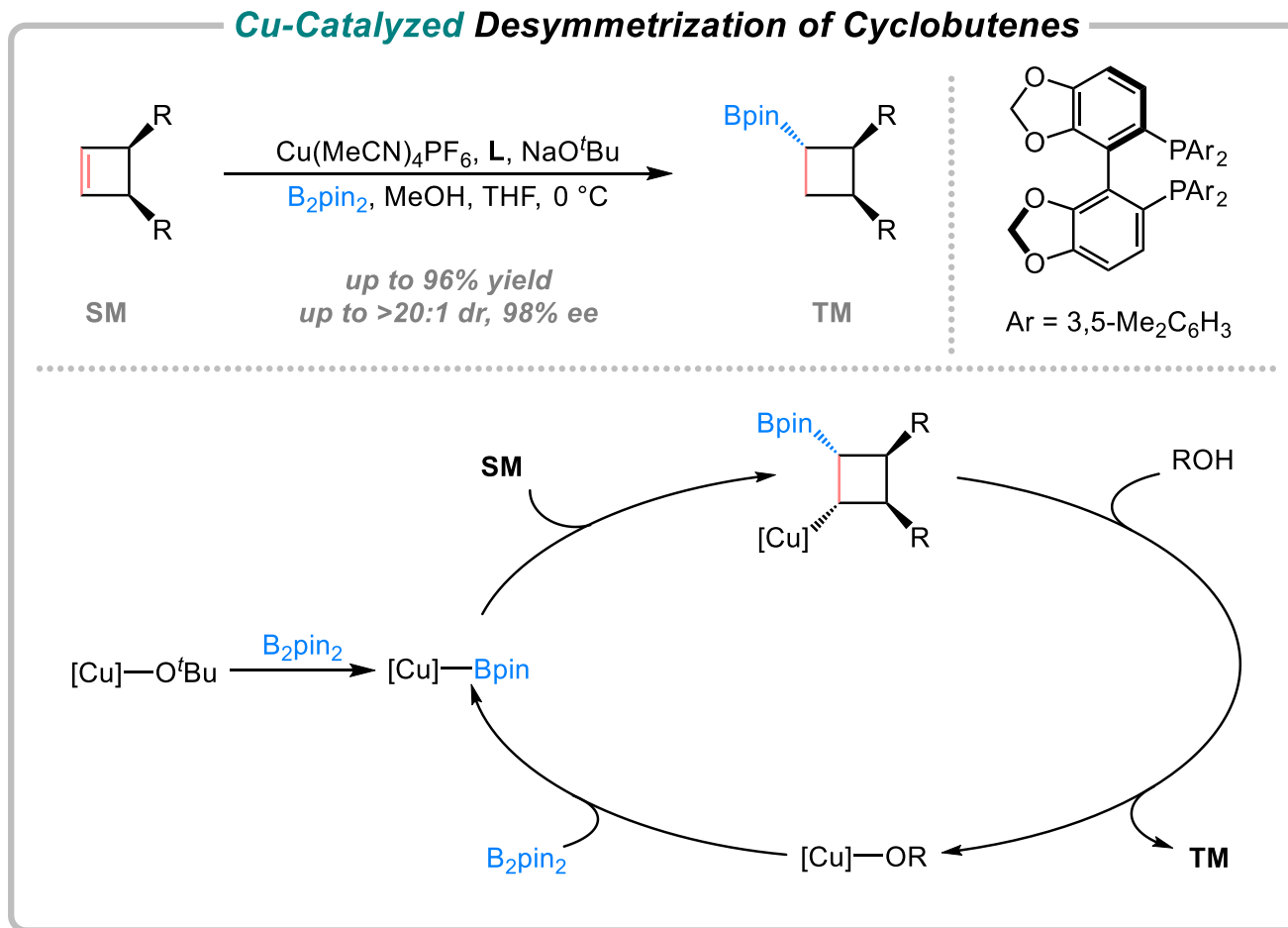


◆ limited to specific electronic and steric properties



◆ precise functionalization allowed

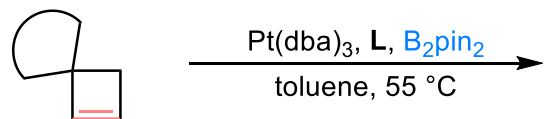
# Introduction



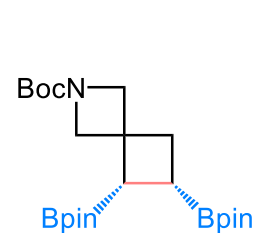
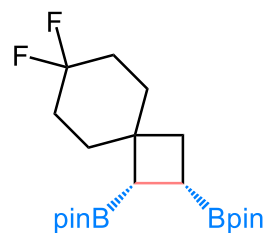
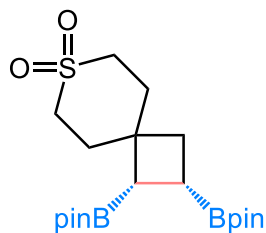
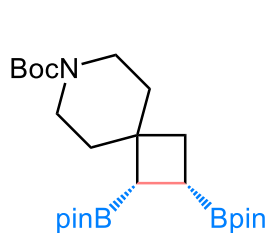
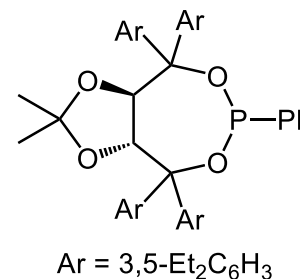
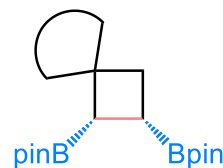
Guisán-Ceinos, M.; Parra, A.; Martín-Heras, V.; Tortosa, M., *Angew. Chem. Int. Ed.* **2016**, *55*, 6969

# Introduction

## *Pt-Catalyzed Enantioselective Dibortation of Cyclobutenes*

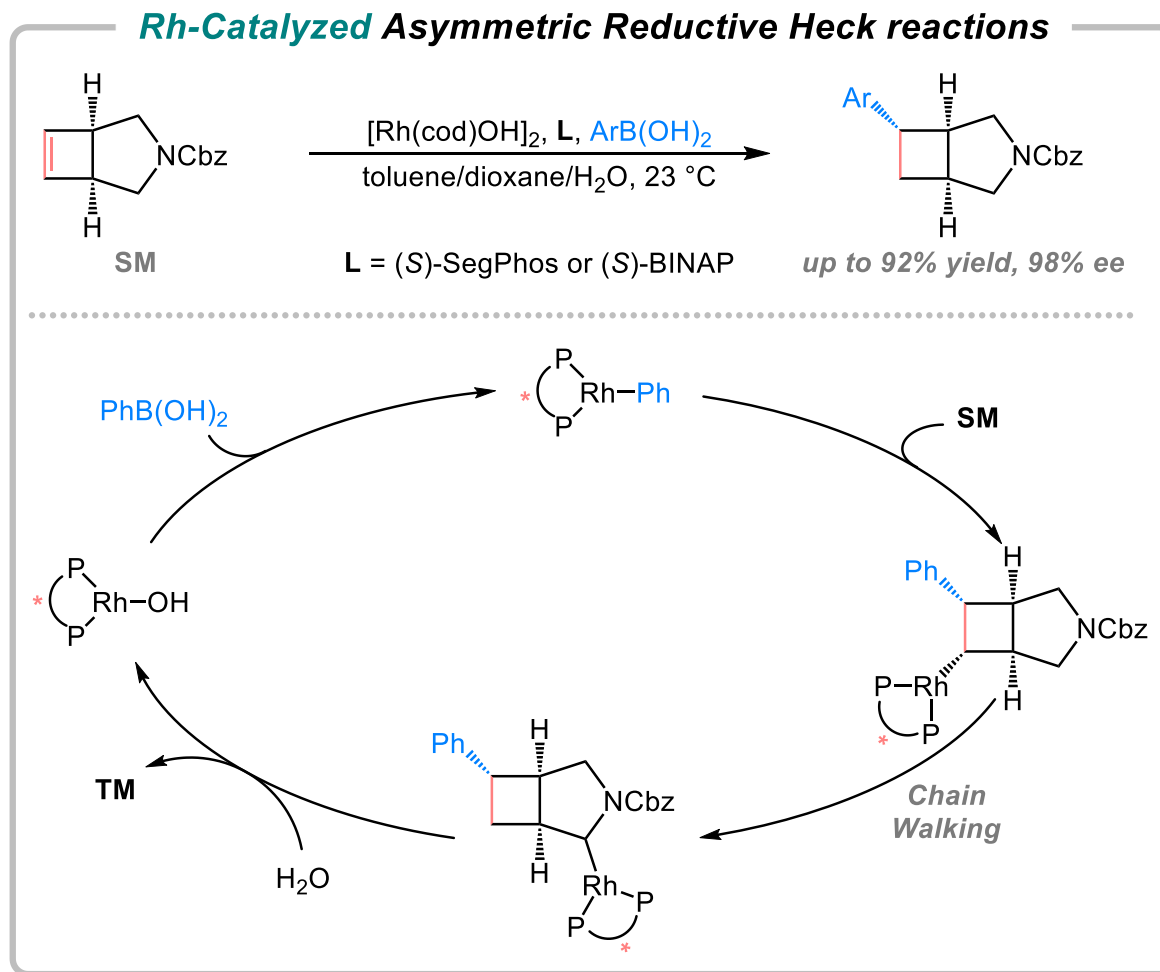


*moderate enantioselectivity*



Nóvoa, L.; Trulli, L.; Parra, A.; Tortosa, M., *Angew. Chem. Int. Ed.* **2021**, *60*, 11763

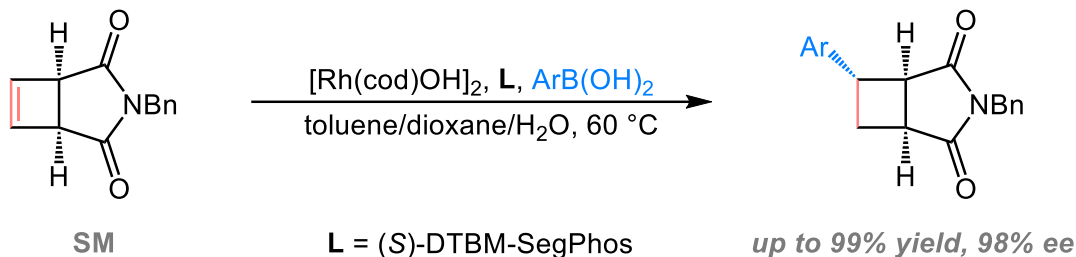
# Introduction



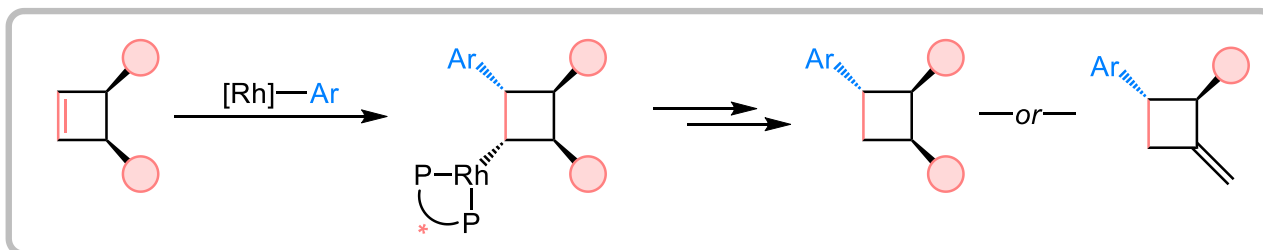
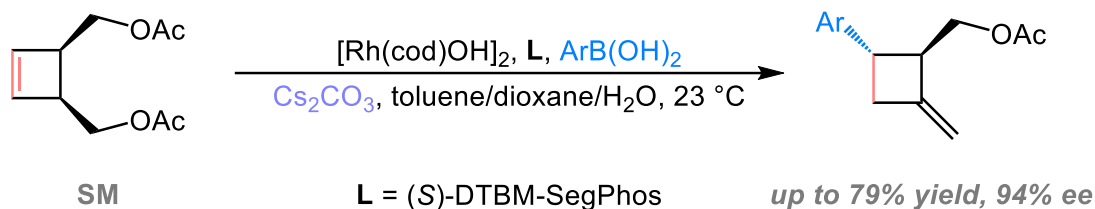
Goetzke, F. W.; Hell, A. M. L.; van Dijk, L.; Fletcher, S. P., *Nat. Chem.* **2021**, 13, 880

# Introduction

## *Rh-Catalyzed Asymmetric Addition*



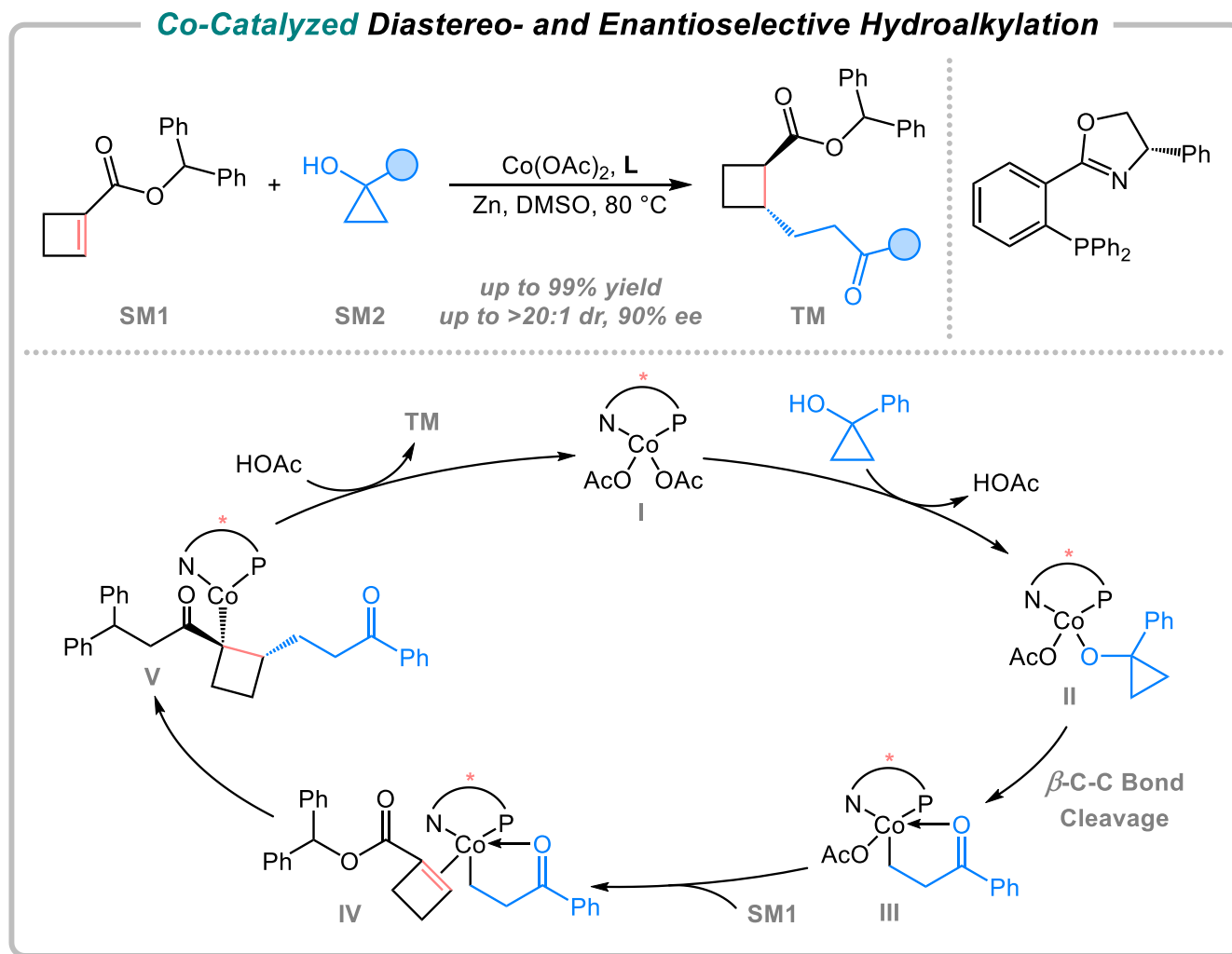
## *Rh-Catalyzed Asymmetric Remote Substitution*



Goetzke, F. W.; Hell, A. M. L.; van Dijk, L.; Fletcher, S. P., *Nat. Chem.* **2021**, 13, 880

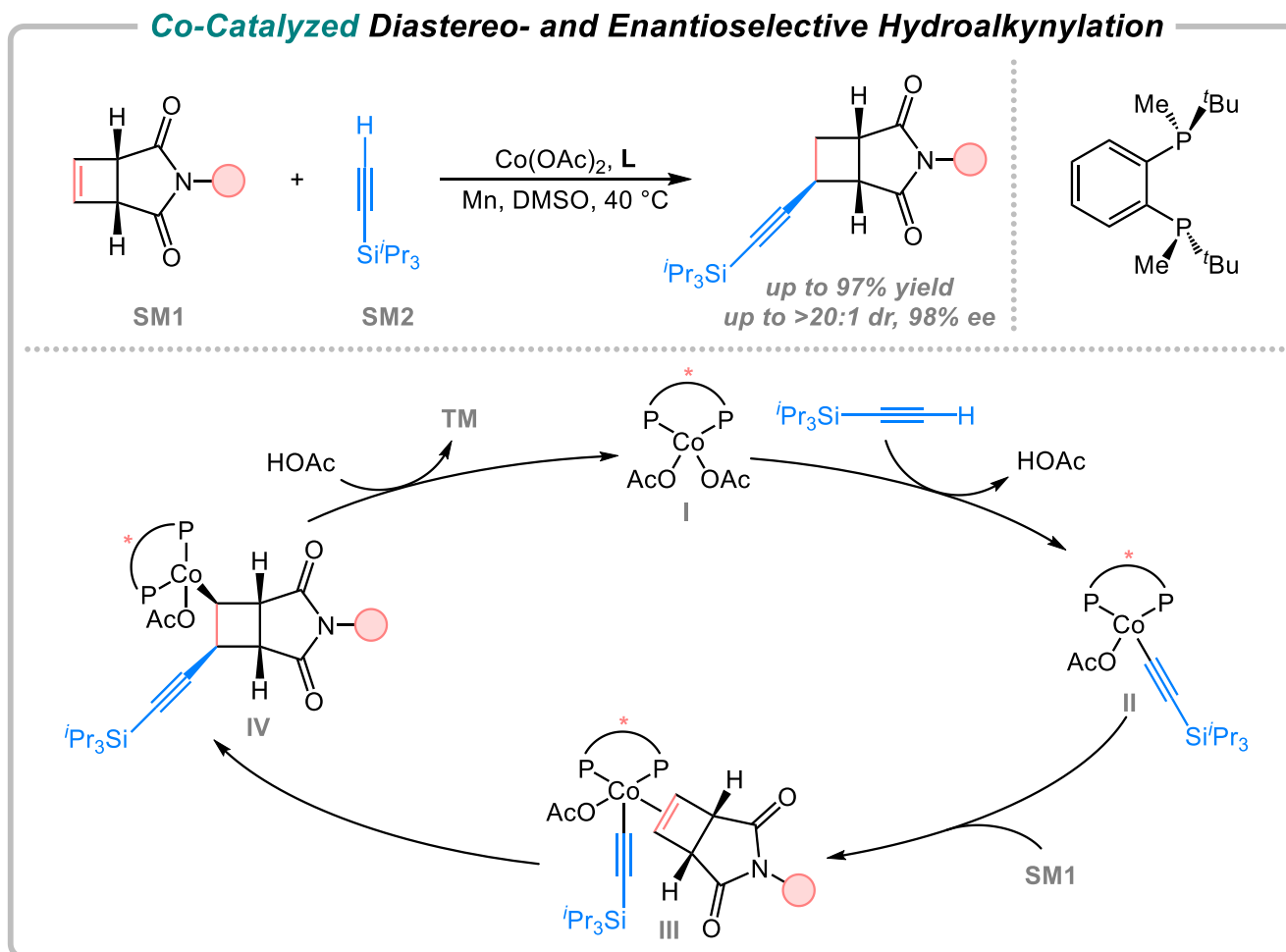


# Introduction



Liang, Z.; Wang, L.; Wang, Y.; Wang, L.; Chong, Q.; Meng, F., *J. Am. Chem. Soc.* **2023**, *145*, 3588

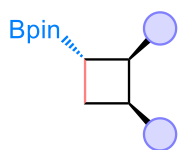
# Introduction



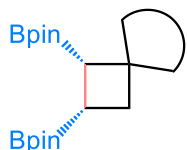
Liang, Z.; Wang, L.; Wang, Y.; Wang, L.; Chong, Q.; Meng, F., *J. Am. Chem. Soc.* **2023**, *145*, 3588

# Current Research Status

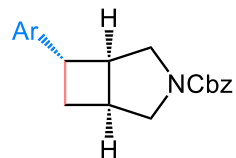
## Enantioselective Functionalization of Cyclobutenes



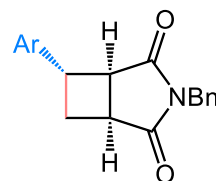
Tortosa, 2016, [Cu]



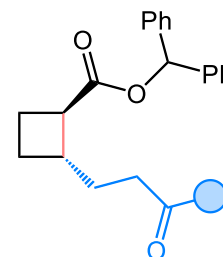
Tortosa, 2021, [Pt]



Fletcher, 2021, [Rh]



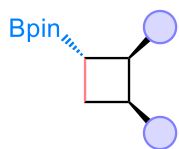
Fletcher, 2021, [Rh]



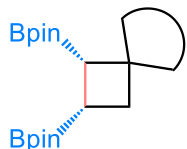
Meng, 2023, [Co]

# Current Research Status

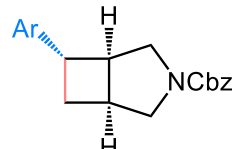
## Enantioselective Functionalization of Cyclobutenes



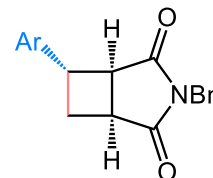
Tortosa, 2016, [Cu]



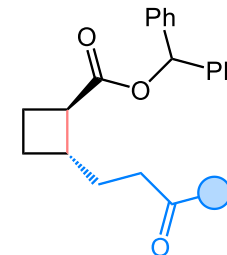
Tortosa, 2021, [Pt]



Fletcher, 2021, [Rh]

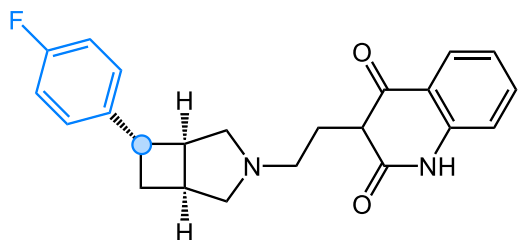


Fletcher, 2021, [Rh]

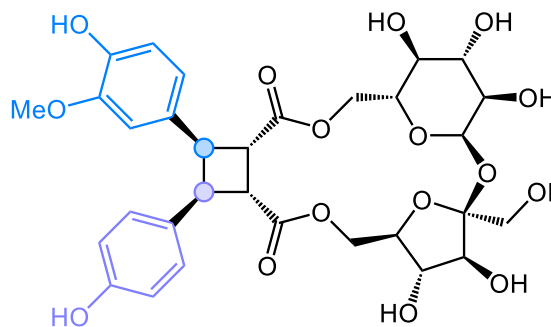


Meng, 2023, [Co]

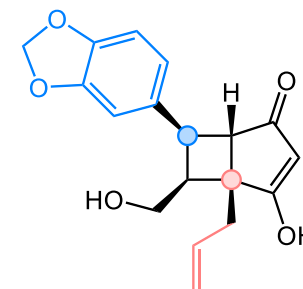
## Representative Bioactive Cyclobutanes



belaperidone

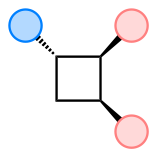


trigohonbanoside D

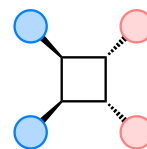


madangone B

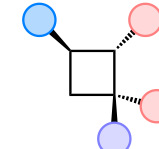
**Pattern A**  
Has Been Reported



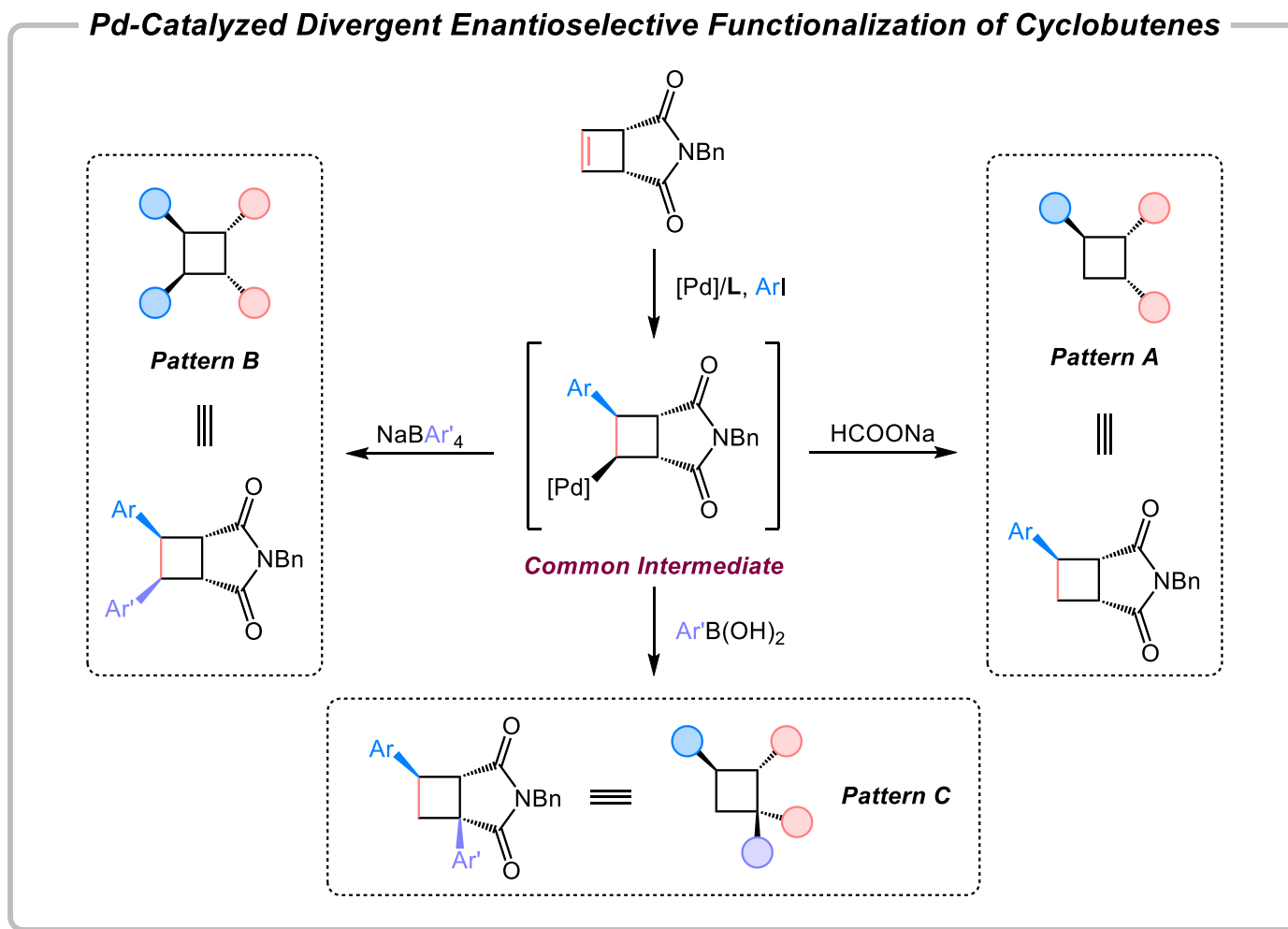
**Pattern B**  
No Report



**Pattern C**  
No Report

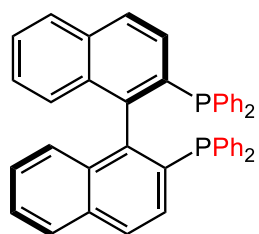
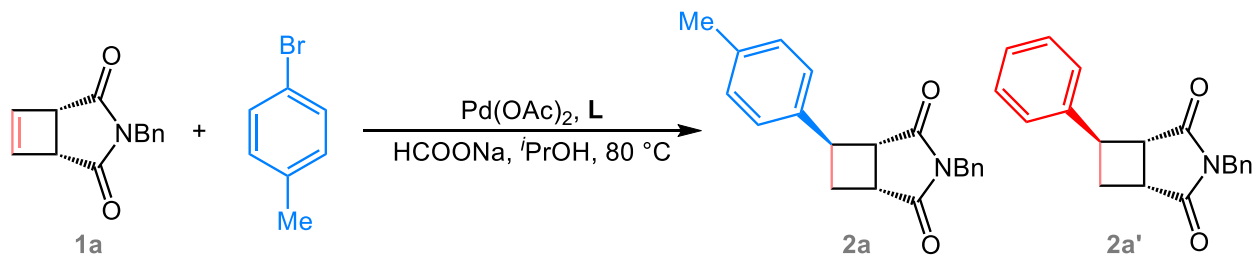


# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

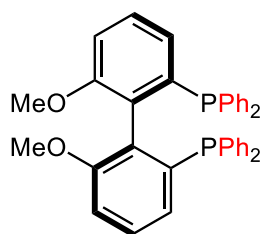


# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

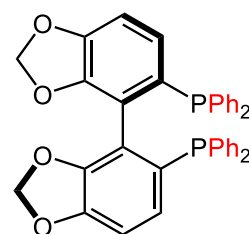
## Optimization of Reductive Heck Reaction (Pattern A)



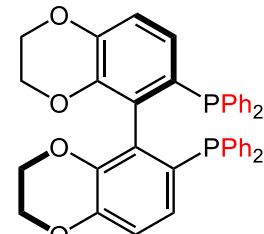
58% **2a**, 12% **2a'**



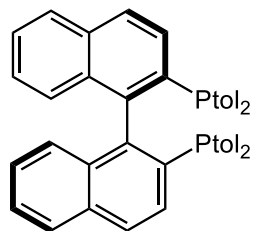
57% **2a**, 11% **2a'**



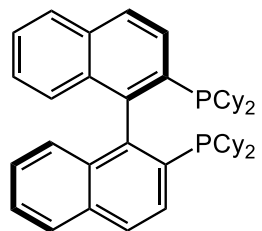
65% **2a**, 10% **2a'**



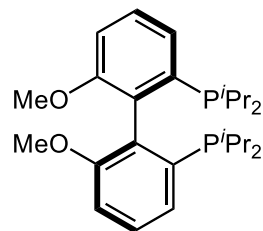
63% **2a**, 12% **2a'**



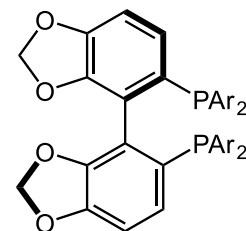
31% **2a**, rac



28% **2a**, 2% ee



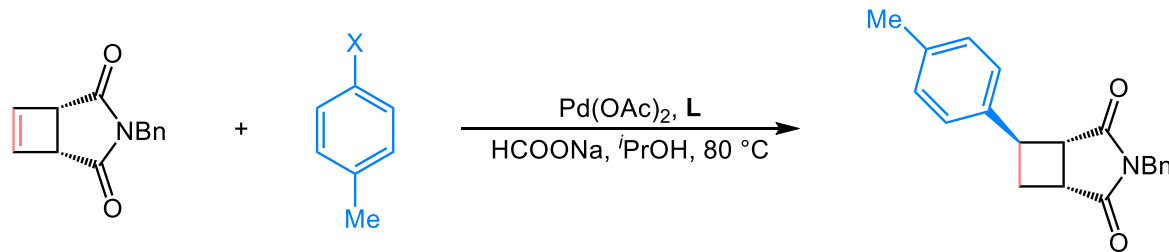
<10%, n.d.



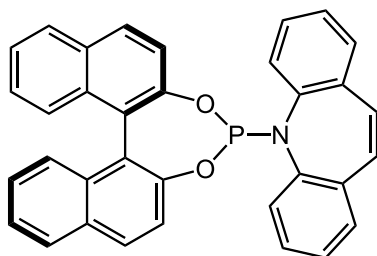
Ar = 3,5-*t*Bu<sub>2</sub>-4-MeOC<sub>6</sub>H<sub>2</sub>  
42% **2a**, rac

# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

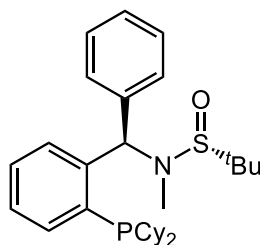
## Optimization of Reductive Heck Reaction (Pattern A)



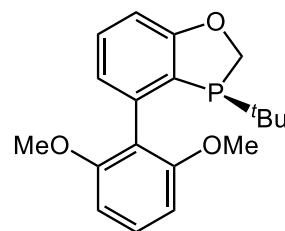
**X = Br**



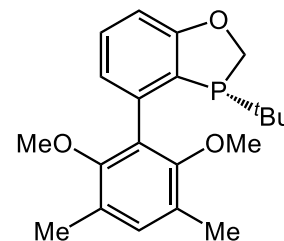
**L1**, 25%, 8% ee



**L2**, 21%, 21% ee

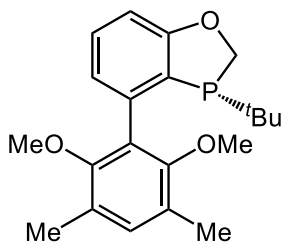


**L3**, 72%, 15% ee

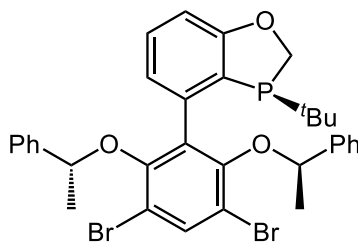


**L4**, 55%, -61% ee

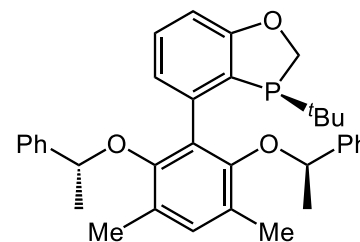
**X = I**



**L4**, 29%, -71% ee



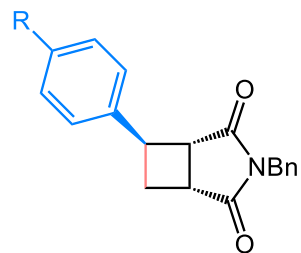
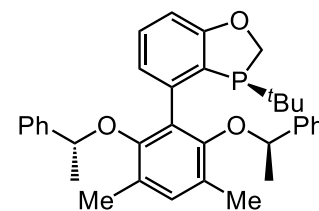
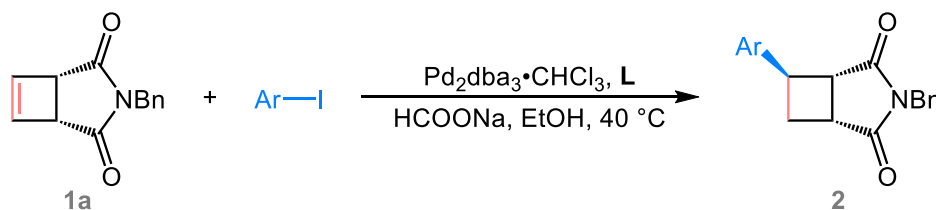
**L5**, 58%, 86% ee ( $60\text{ }^\circ\text{C}$ )



**L6**, 82%, 91% ee  
( $40\text{ }^\circ\text{C}$ ,  $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ , EtOH)

# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

## Substrate Scope of the Reductive Heck Reaction (Pattern A)



**2b**, R = H, 77%, 88% ee

**2c**, R = OMe, 73%, 92% ee

**2d**, R = OH, 70%, 96% ee

**2f**, R = *i*Pr, 89%, 90% ee

**2g**, R = Ph, 90%, 88% ee

<sup>a</sup>Pd(TFA)<sub>2</sub>, *i*PrOH, 50 °C

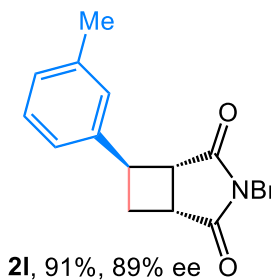
**2e**, R = NHBoc, 85%, 92% ee

**2h**, R = F, 79%, 88% ee<sup>a</sup>

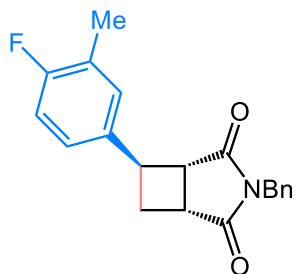
**2i**, R = Cl, 64%, 87% ee<sup>a</sup>

**2j**, R = Br, 47%, 88% ee<sup>a</sup>

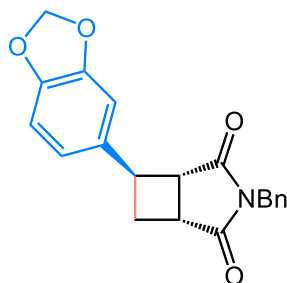
**2k**, R = CO<sub>2</sub>Me, 82%, 81% ee<sup>a</sup>



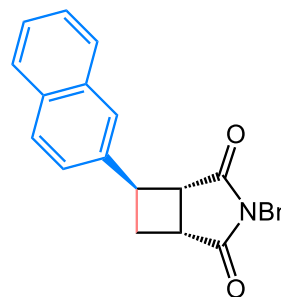
**2l**, 91%, 89% ee



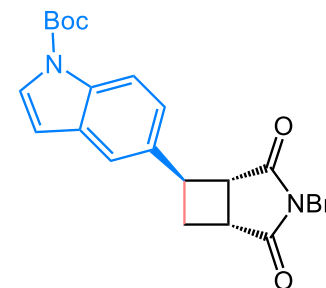
**2n**, 84%, 90% ee



**2o**, 53%, 91% ee



**2p**, 73%, 89% ee

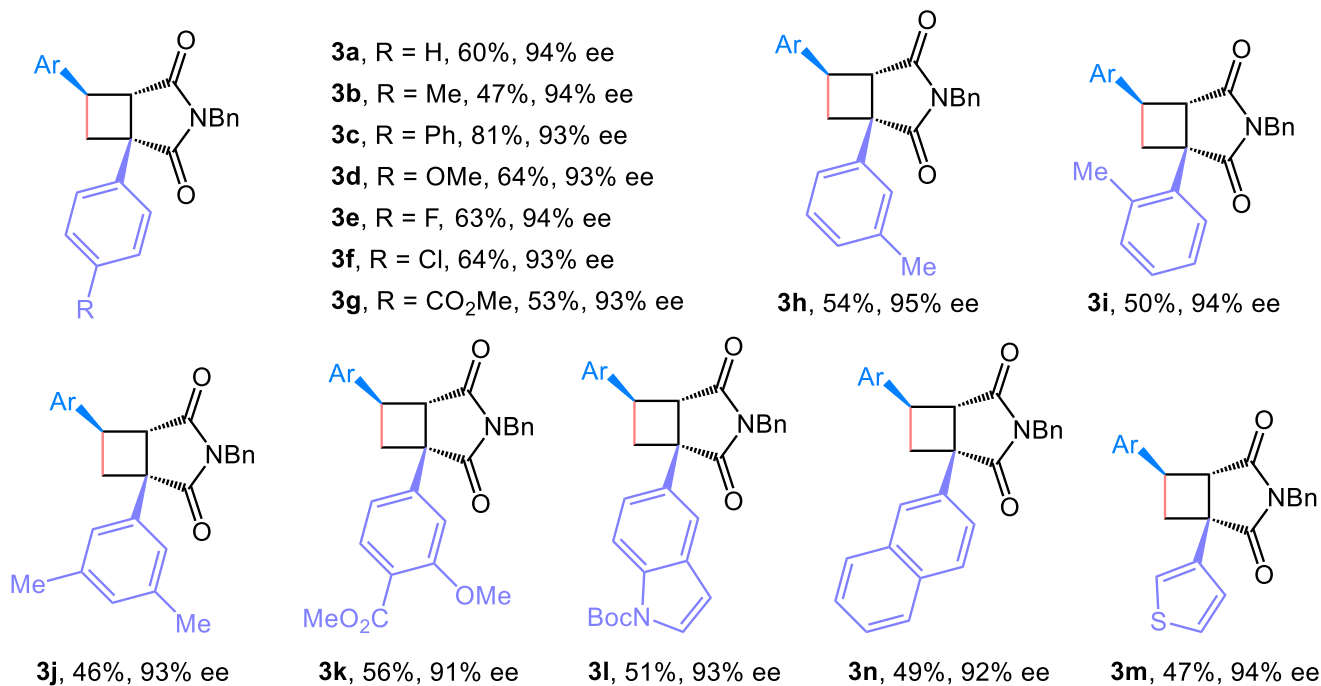
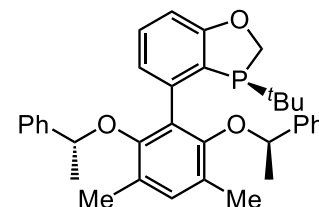
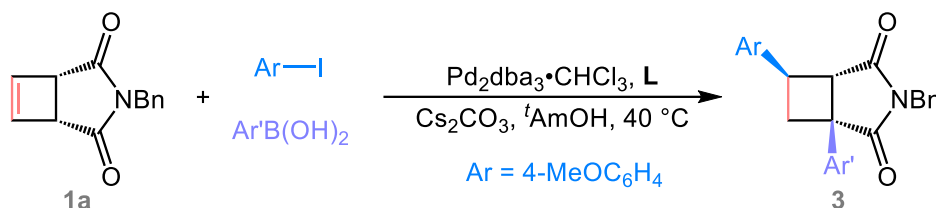


**2r**, 75%, 92% ee



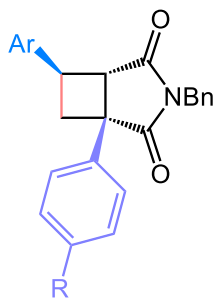
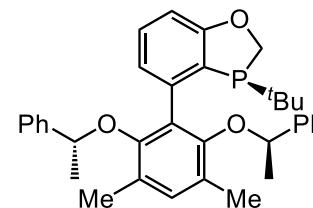
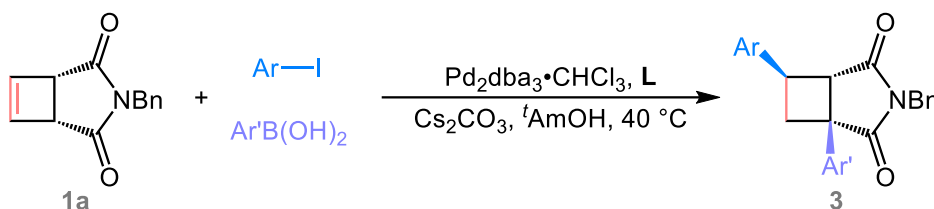
# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

## Substrate Scope of the 1,3-Diarylation (Pattern C)



# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

## Substrate Scope of the 1,3-Diarylation (Pattern C)



<sup>a</sup>K<sub>3</sub>PO<sub>4</sub> instead of Cs<sub>2</sub>CO<sub>3</sub>; <sup>b</sup>Pd(TFA)<sub>2</sub>, K<sub>3</sub>PO<sub>4</sub>, 50 °C

**Ar = 4-MeC<sub>6</sub>H<sub>4</sub>**

**3o**, R = H, 70%, 93% ee<sup>a</sup>

**3p**, R = Me, 49%, 94% ee<sup>a</sup>

**3q**, R = CO<sub>2</sub>Me, 73%, 92% ee

**Ar = C<sub>6</sub>H<sub>5</sub>**

**3r**, R = H, 65%, 92% ee<sup>a</sup>

**3s**, R = Me, 62%, 92% ee<sup>a</sup>

**3t**, R = CO<sub>2</sub>Me, 60%, 91% ee

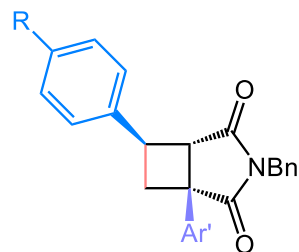
**Ar = 4-MeO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>**

**3u**, R = H, 73%, 82% ee<sup>b</sup>

**3v**, R = OMe, 53%, 84% ee<sup>b</sup>

**3w**, R = CO<sub>2</sub>Me, 68%, 79% ee<sup>b</sup>

**Ar' = 4-MeO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>**



**3x**, R = NHBoc, 65%, 91% ee

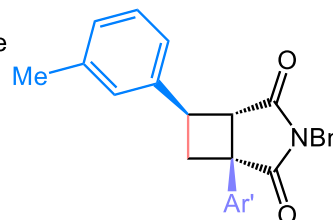
**3y**, R = <sup>i</sup>Pr, 72%, 91% ee

**3z**, R = Ph, 45%, 89% ee

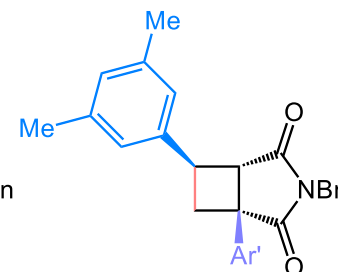
**3aa**, R = Cl, 72%, 87% ee<sup>c</sup>

**3ab**, R = F, 74%, 87% ee<sup>c</sup>

<sup>c</sup>Pd(TFA)<sub>2</sub>, Cs<sub>2</sub>CO<sub>3</sub>, 50 °C



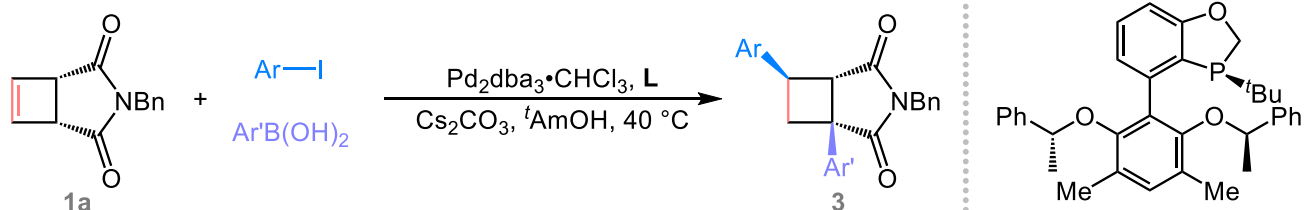
**3ac**, 73%, 94% ee



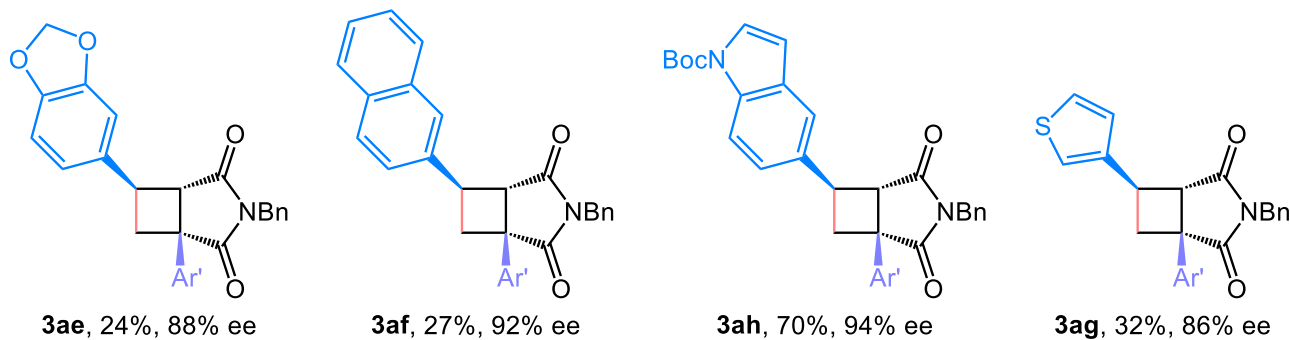
**3ad**, 75%, 96% ee

# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

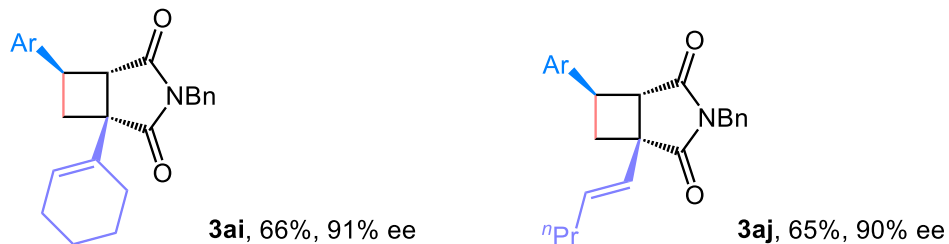
## Substrate Scope of the 1,3-Diarylation (Pattern C)



Ar' = 4-MeO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

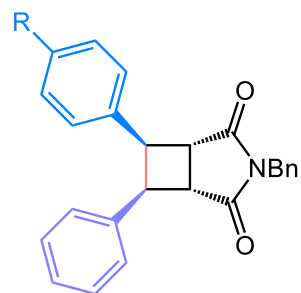
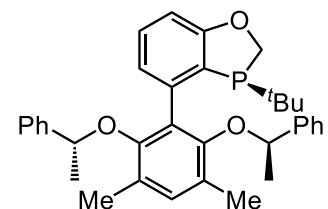
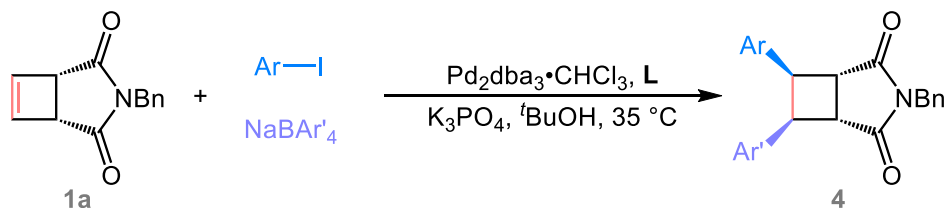


Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>



# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

## Substrate Scope of the 1,2-Diarylation (Pattern B)



**4a**,  $\text{R} = \text{Me}$ , 69%, 91% ee

**4b**,  $\text{R} = i\text{Pr}$ , 99%, 86% ee

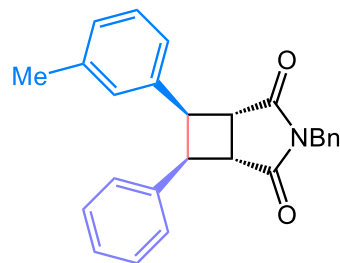
**4c**,  $\text{R} = \text{Ph}$ , 90%, 86% ee

**4d**,  $\text{R} = \text{OMe}$ , 95%, 86% ee

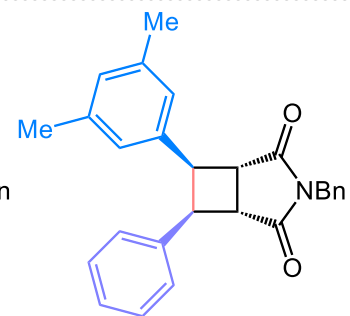
**4e**,  $\text{R} = \text{NH}^t\text{Boc}$ , 98%, 86% ee

**4f**,  $\text{R} = \text{F}$ , 70%, 82% ee

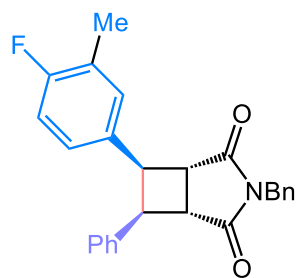
**4g**,  $\text{R} = \text{CO}_2\text{Me}$ , 55%, 60% ee



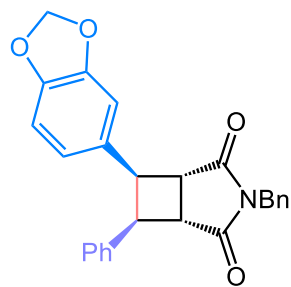
**4h**, 96%, 93% ee



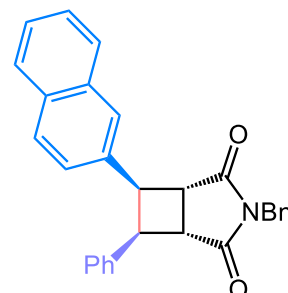
**4i**, 99%, 93% ee



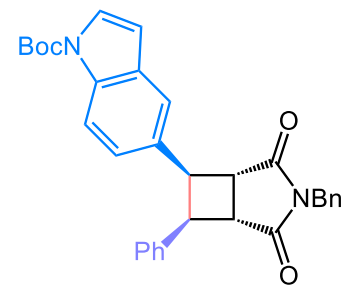
**4j**, 79%, 90% ee



**4k**, 80%, 88% ee



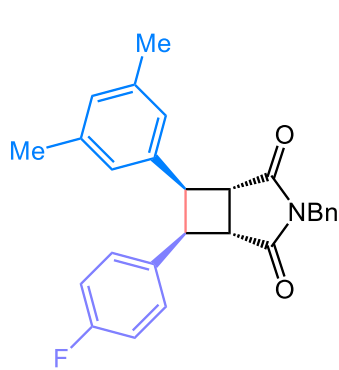
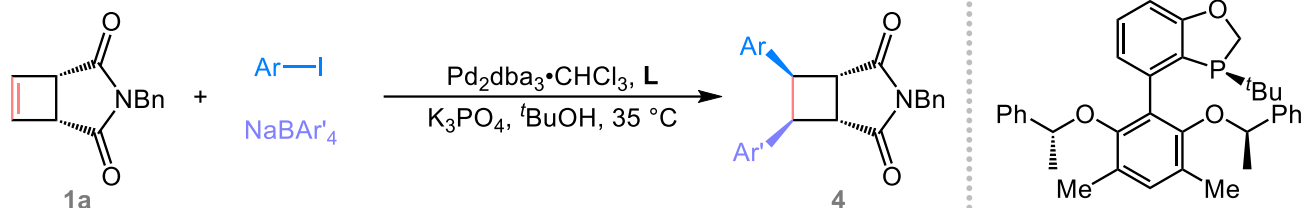
**4l**, 86%, 86% ee



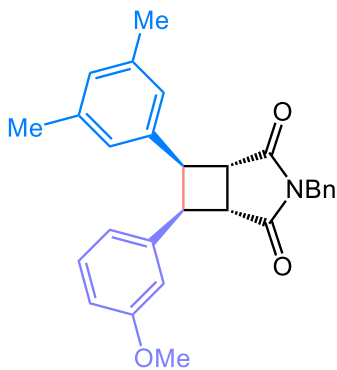
**4m**, 96%, 94% ee

# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

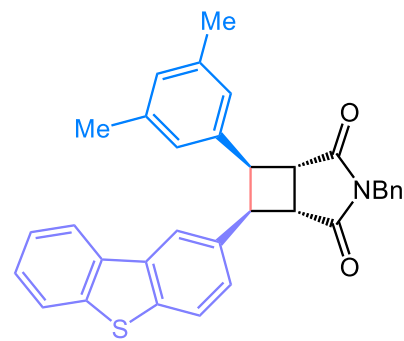
## Substrate Scope of the 1,2-Diarylation (Pattern B)



**4n**, 68%, 92% ee



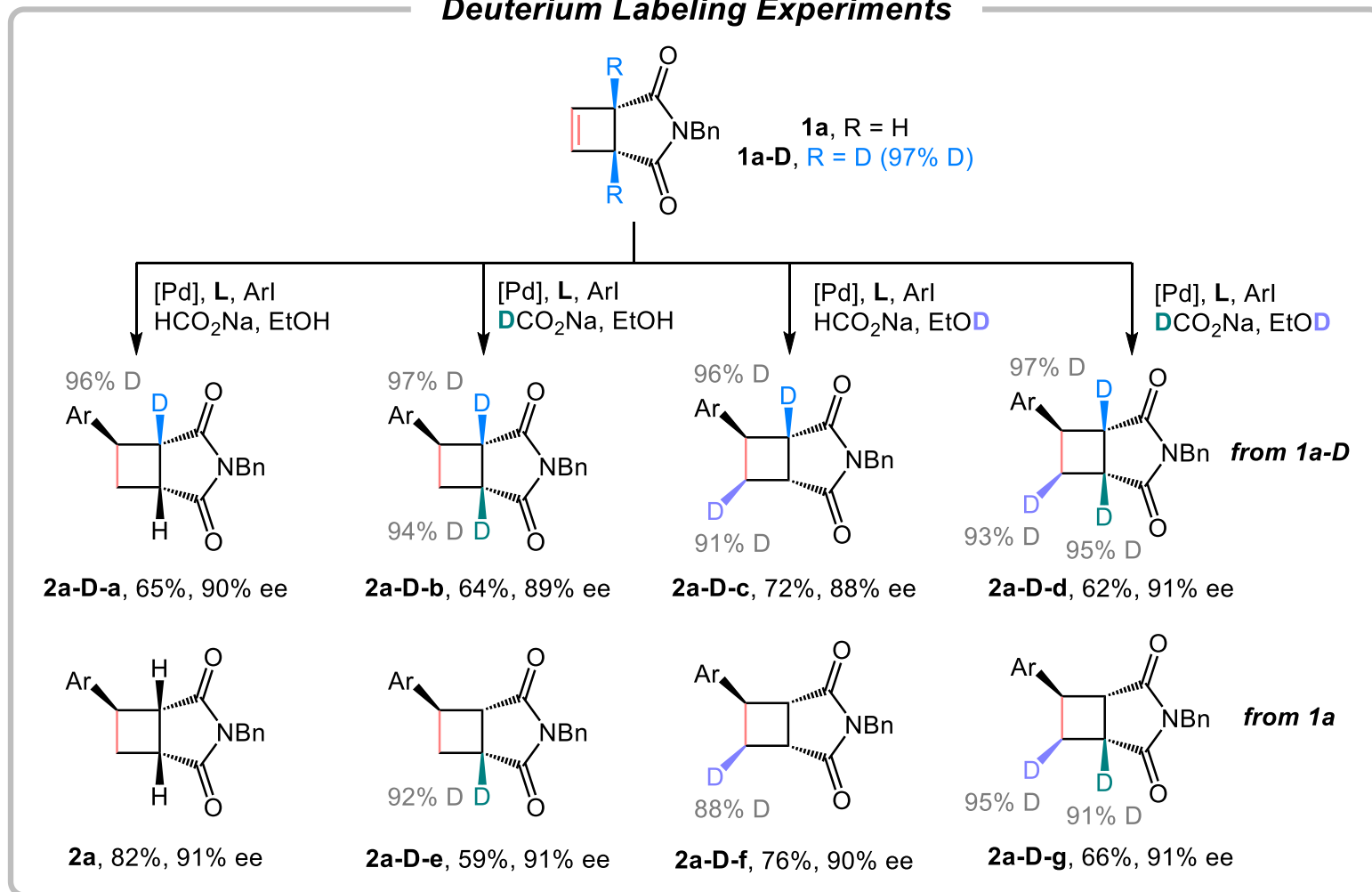
**4p**, 84%, 81% ee



**4q**, 70%, 57% ee

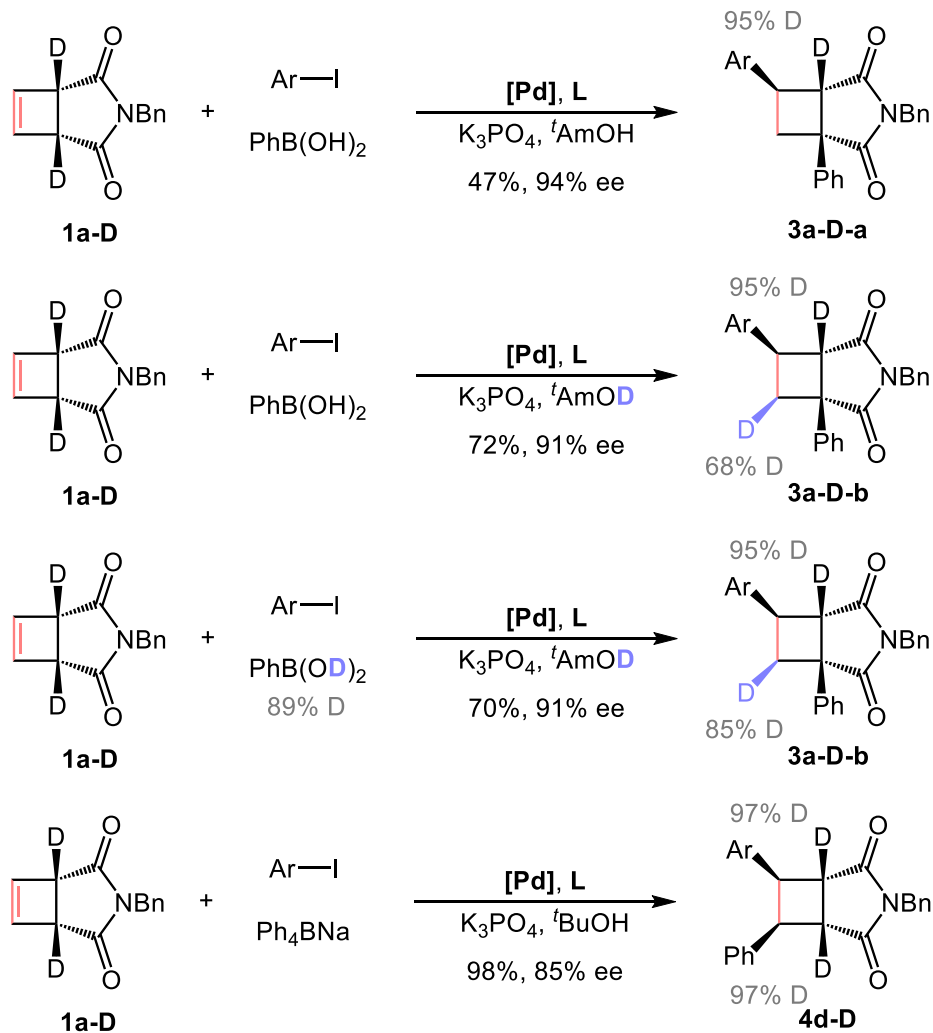
# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

## Deuterium Labeling Experiments



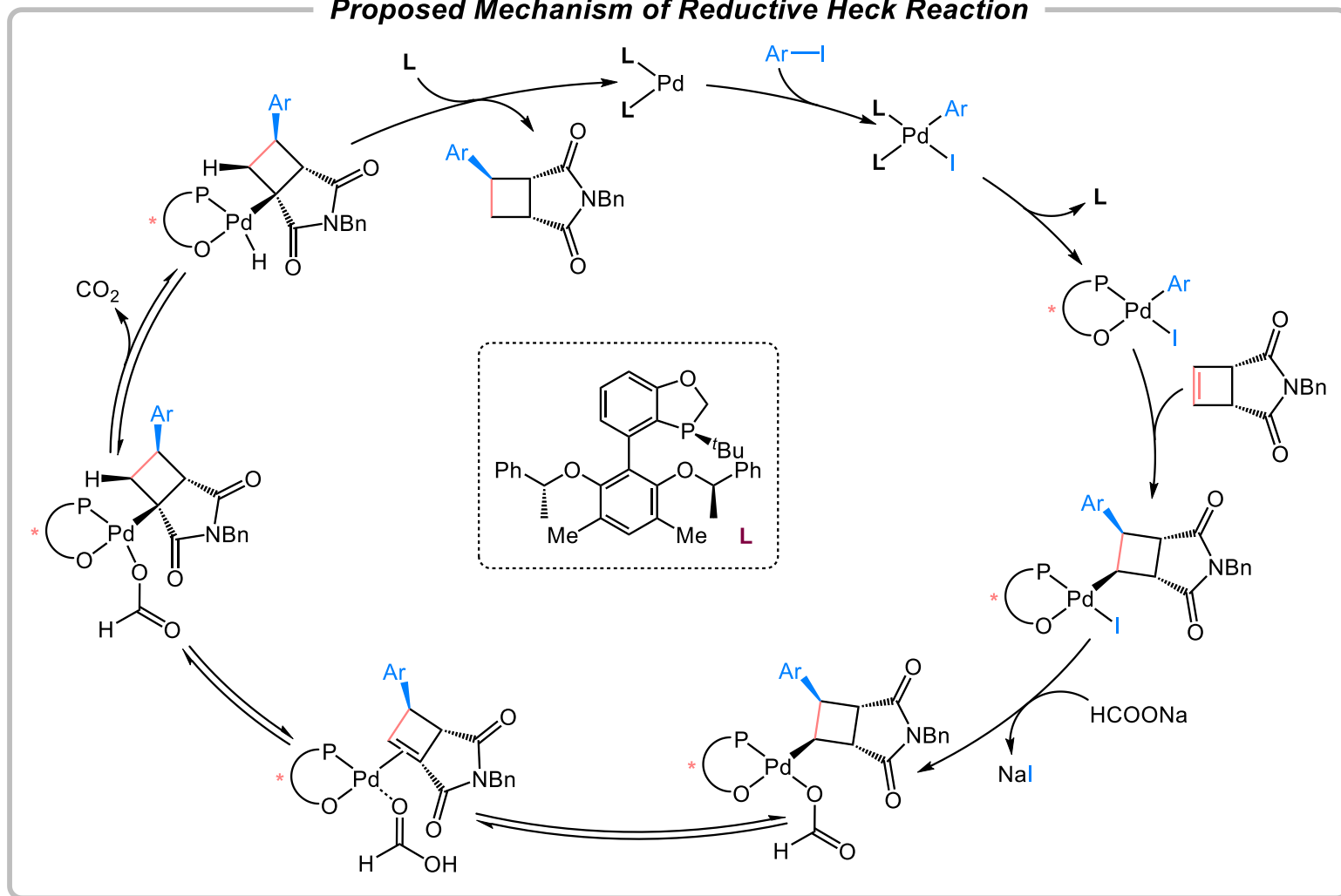
# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

## Deuterium Labeling Experiments



# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

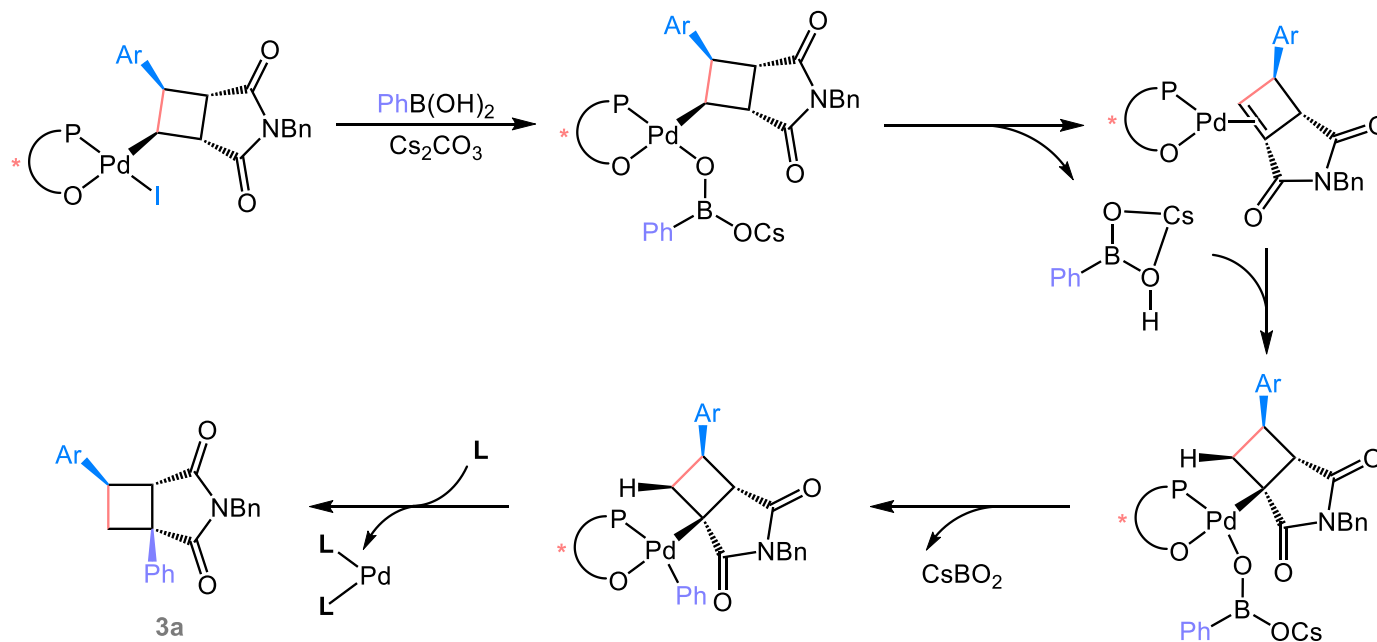
## Proposed Mechanism of Reductive Heck Reaction



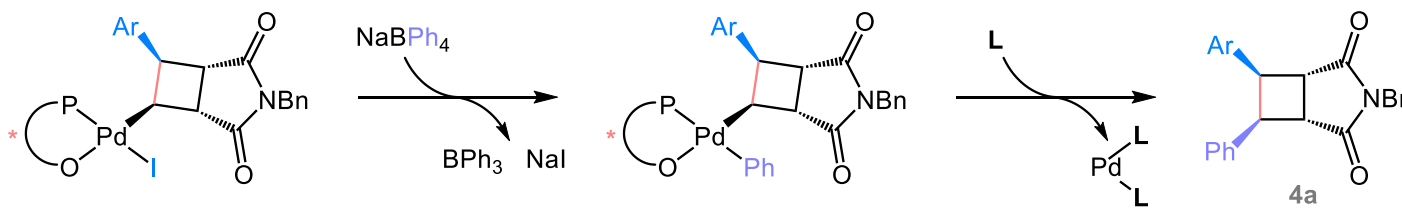


# Pd-Catalyzed Enantioselective Functionalization of Cyclobutenes

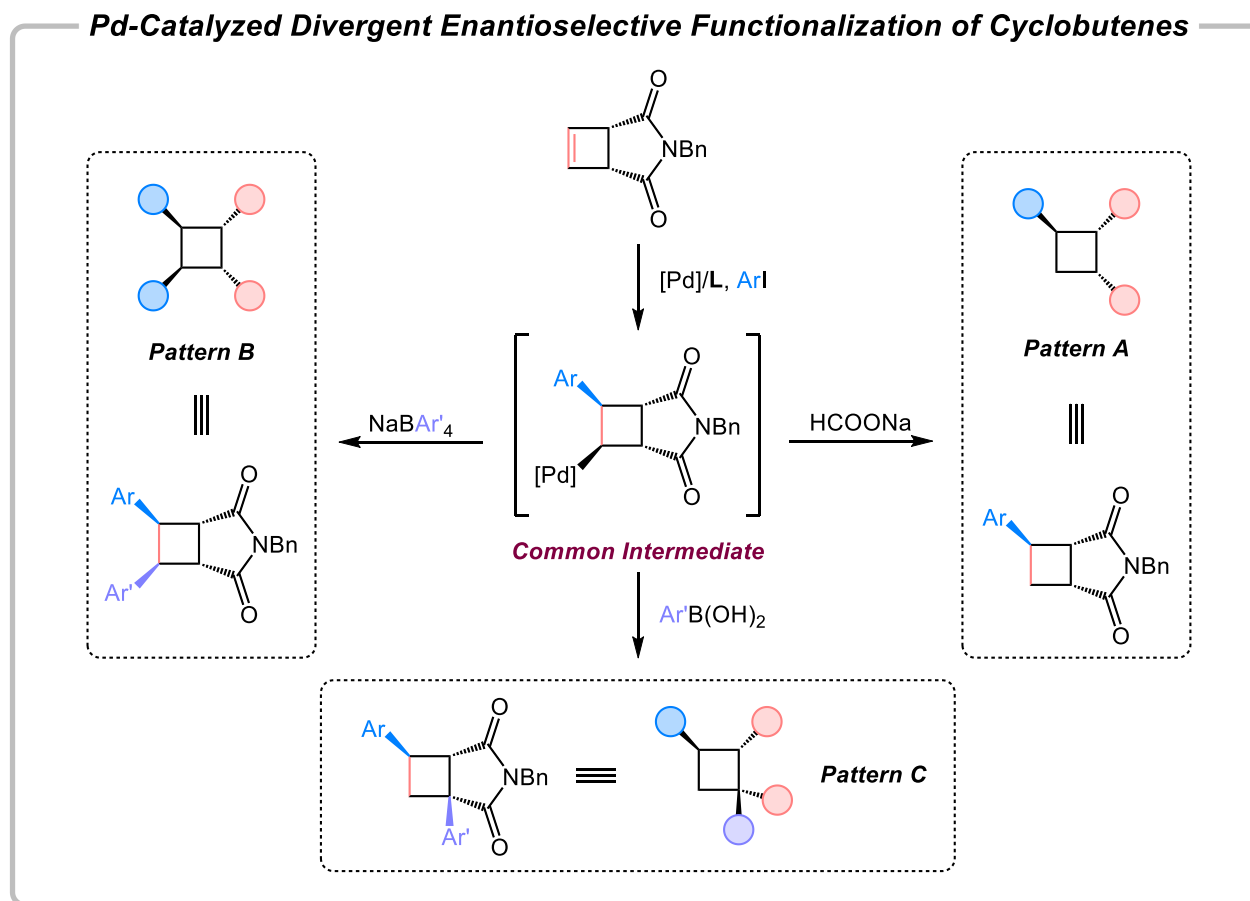
## Proposed Pathway for the Formation of 3a



## Proposed Pathway for the Formation of 4a



# Summary



»» **Interceptions of a Common Heck Intermediate**

»» **Reductive Heck & 1,3-Diarylation & 1,2-Diarylation—Divergent Functionalization**

# Writing Strategies

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## □ The First Paragraph

The **Importance** of  
Chiral Cyclobutanes



**Construction** of  
Chiral Cyclobutanes



Current Limits and  
**New Strategy**

- ✓ Aliphatic small rings, including cyclopropanes and cyclobutanes, have been increasingly investigated in medicinal chemistry for their beneficial physicochemical properties. **Cyclobutanes containing multiple contiguous chiral centers have demonstrated appealing bioactivities.**
- ✓ Although enantioselective **[2 + 2]-photocycloaddition** is a straightforward strategy to access chiral cyclobutane derivatives, the structural diversity is limited, as it generally requires two alkenes with matched electronic and steric properties. As a class of readily available carbocycles, **cyclobutene** has been used to synthesize enantioenriched cyclobutane derivatives.
- ✓ A highly enantioselective difunctionalization of cyclobutenes for the syntheses of **Pattern B and C cyclobutanes is still underdeveloped.** Here, we report our work on palladium-catalyzed divergent enantioselective **functionalization of strained alkene cyclobutene** to the assembly of the above multisubstituted Pattern A–C cyclobutanes

# Writing Strategies

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## □ The Last Paragraph

### Summary of this Work



### Highlights of this Work



### Outlook of this Work

- ✓ In conclusion, we developed here a **divergent** palladium-catalyzed desymmetrization of cyclobutene to access enantioenriched multi-substituted cyclobutanes with **three substitution patterns**.
- ✓ Three types of enantioselective reactions, including the **reductive Heck reaction**, **1,3-arylation**, and **1,2-arylation**, were developed from the common Heck intermediate with the evolution of the P-chiral ligand. A variety of deuterated Heck reductive products could be obtained with the judicious choice of deuterated reagents and solvents, demonstrating its potential utility in medicinal chemistry.
- ✓ We envision that the investigation of the precise functionalization of the preformed four-membered ring skeleton could **reveal more characteristic and valuable transformations** with the development of a new methodology.

# Representative Examples

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- ✓ Even non-enantioselective carbometallation approaches for four-membered rings are **nontrivial** (*adj.* 非平凡的, 重要的) and rare.
- ✓ With ortho-substituted arylboronic acids, which often **suffer from** (遭受, 忍受, 可用于形容反应中存在的问题) low yields and enantioselectivity in transition-metal-catalyzed reactions, we obtained low enantioselectivity using standard conditions.
- ✓ As **depicted** (*vt.* 描绘, 描画) in Figure 1A, cyclobutanes containing multiple contiguous chiral centers have demonstrated appealing bioactivities.

# Acknowledgement

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*Thanks for your attentions!*